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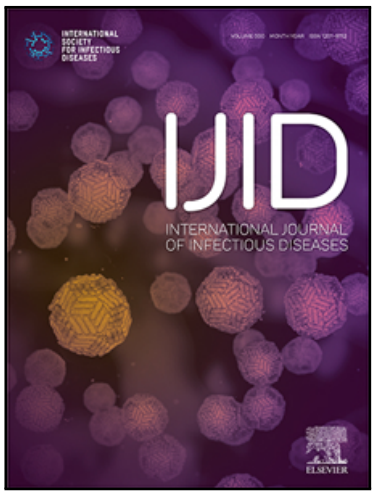

Clinical Characteristics of Patients with Coronavirus Disease (COVID-19): Preliminary Baseline Report of Japan COVID-19 Task Force, a Nation-wide Consortium to Investigate Host Genetics of COVID-19

Hiromu Tanaka , Ho Lee , Atsuho Morita , Ho Namkoong , Shotaro Chubachi , Hiroki Kabata , Hirofumi Kamata , Makoto Ishii , Naoki Hasegawa , Norihiro Harada , Tetsuya Ueda , Soichiro Ueda , Takashi Ishiguro , Ken Arimura , Fukuki Saito , Takashi Yoshiyama , Yasushi Nakano , Yoshikazu Mutoh , Yusuke Suzuki , Koji Murakami , Yukinori Okada , Ryuji Koike , Yuko Kitagawa , Katsushi Tokunaga , Akinori Kimura , Seiya Imoto , Satoru Miyano , Seishi Ogawa , Takanori Kanai , Koichi Fukunaga , The Japan COVID-19 Task Force

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Highlights:

- Patients with COVID-19 were recruited from more than 70 institutes in Japan.
- Japan experienced 3 waves of COVID-19 during the first year of the pandemic.
- The case fatality rate of 3.2% was relatively low.
- The data will be used for a genome-wide association study.

Clinical Characteristics of Patients with Coronavirus Disease (COVID-19): Preliminary Baseline Report of Japan COVID-19 Task Force, a Nation-wide Consortium to Investigate Host Genetics of COVID-19

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Abstract

Background and design:

The coronavirus disease (COVID-19) pandemic is having a devastating effect worldwide. Host genome differences between populations may influence the severity of COVID-19.

The Japan COVID-19 Task Force is conducting host genome analysis of hospitalized patients with COVID-19 from more than 70 institutions nationwide in Japan. This report describes the clinical characteristics of patients enrolled to date.

Results:

The median (interquartile range) age of the 1674 patients included in the analysis was 59 (45–71) years, and more than half of the patients (66.2%) were male. Less than half of the patients (41.2%) had severe disease. The case fatality rate was 3.2%.

Conclusions:

Since this is a hospital-based study, the number of severe cases was relatively high, but the case fatality rate was relatively low, when compared to that of other

countries. In the future, we will continue to enroll patients and conduct genome analyses of patients with COVID-19.

Keywords: COVID-19, Clinical character, Pneumonia, Host genetics, Japan

The coronavirus disease (COVID-19) pandemic has had a devastating effect worldwide, including in Japan (see https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html). Host genome differences between populations may influence disease severity. This may explain why Asians, including Japanese, may have a lower risk of death (Price-Haywood EG et al., 2020; Zeberg H et al., 2020). The Japan COVID-19 Task Force was established in early 2020 as a nationwide multicenter consortium. We collected and analyzed clinical specimens from patients in more than 70 institutions nationwide since February 2020 and reported the results of a genome-wide association study (Namkoong H et al., 2021).

This cross-sectional study aimed to determine the clinical characteristics of Japanese patients with COVID-19. The study facilities provide coverage for the most populous prefectural capital cities in Japan. We included 1645 (98.3%) patients with reverse transcription polymerase chain reaction (RT-PCR)-confirmed COVID-19, 10 (0.6%) patients with rapid antigen test-confirmed COVID-19, and 19 (1.1%) patients who were considered as highly suspicious for COVID-19 by the physician. We collected information on patient demographics, laboratory test data, radiographic imaging, treatment,

comorbidities, and outcomes for 1674 cases to construct a database for the Japan COVID-19 Task Force. The cases were not limited to inpatients; however, 1668 (99.6%) patients were hospitalized patients. All the patients in this study provided appropriate informed consent, which was approved by the ethics committee of the affiliated institutes. Symptoms and signs included not only those reported on referral or admission but also those observed during hospitalization. Laboratory and radiographic data were collected within 48 hours of the initial visit or admission. Disease outcome during hospitalization was assessed for fatality rate. We obtained information regarding any support using oxygen devices, invasive mechanical ventilation (IMV), and extracorporeal membrane oxygenation (ECMO) during the clinical course to determine the disease severity. In this report, disease severity was defined as follows: most severe, patients requiring support using high-flow oxygen devices, IMV, ECMO, or death; severe, patients requiring support using low-flow oxygen devices; mild, symptomatic patients not requiring oxygen support; asymptomatic, asymptomatic patients not requiring oxygen support (World Health Organization, 2020).

The patients' clinical characteristics are shown in Table 1. Their median

(interquartile range) age was 59 (45–71) years, 66.2% were male, and most patients were Japanese. Comorbidities included hypertension (34.6%), diabetes mellitus (22.9%), coronary artery disease (9.9%), and chronic kidney disease (7.0%). Moreover, 231 cases were categorized as most severe (13.8%), 459 cases as severe (27.4%), 933 cases as mild (55.7%), and 51 cases as asymptomatic (3.0%). The most common symptom was fever (≥37.5°C), which was observed in 79.3% of patients. Cough, sputum, shortness of breath, dysgeusia, and dysosmia were observed in 58.2%, 24.7%, 30.7%, 18.7%, and 17.0% of patients, respectively. Most patients were enrolled in April 2020 (first wave), August 2020 (second wave), and December 2020 (third wave) (Figure 1). Supplementary Table 1 shows the patients' characteristics in each epidemic. There was a high prevalence of elderly males among patients in the third epidemic. They also had a higher prevalence of comorbidities such as hypertension, diabetes, and chronic kidney disease, and a low prevalence of dysgeusia and dysosmia.

Laboratory findings showed an elevated inflammatory response, with median ferritin and C-reactive protein levels of 376 ng/mL and 2.69 mg/dL, respectively. Regarding radiographic findings, 81.3% of patients had ground

glass opacity (GGO), and 39.8% had consolidation on chest computed tomography. The bilateral spread of GGOs was generally present during the acute phase of COVID-19.

A total of 19.0% of patients were admitted to the intensive care unit, 11.1% were intubated, and 2.3% required ECMO. The fatality rate was 3.2%. Complications included bacterial infection and thrombosis in 11.9% and 3.6% of patients, respectively. The most commonly used antivirals were favipiravir and remdesivir, which were used in 35.9% and 18.9% of patients, respectively. Systemic corticosteroids were used in 40.9% of patients, especially in 58.9% of patients in the third epidemic.

Clinical characteristic of patients in this study were similar to those of other previously reported large-sample studies in Asian populations (Guan WJ et al., 2020; Matsunaga N et al., 2020). The proportion of male patients was higher in this study than in other studies, which may be due to the relatively high disease severity in males (Chen N et al., 2020). The proportion of patients with comorbidities such as hypertension, diabetes, and chronic kidney disease, was higher than that reported in another registry in Japan (Matsunaga N et al., 2020). We believe that this finding is due to a large number of patients registered in the

third epidemic, unlike the situation in the previously reported registry. Our study suggests that the number of hospitalized older male patients with more comorbidities has gradually increased in Japan during the past year. Compared with the recent meta-analyses in other countries (Macedo A et al., 2021), we believe that the lower fatality rate in this study and in the previous report (Matsunaga N et al., 2020) may be explained by reasons specific to Japan. We consider the possibility that many inpatient cases of our study would have been treated as outpatients in other countries, because in Japan, the public health centers coordinated the hospitalization of many patients, including those with mild disease. The low fatality rate may also reflect the unique genetic characteristics of the Japanese. For example, the effect of DOCK2 on disease severity of COVID-19 has been reported (Namkoong H et al., 2021). Our study had a large group of patients treated with remdesivir, especially in the third epidemic. A relatively high proportion of patients were treated with systemic corticosteroids, based on the results of the RECOVERY trial (Horby P et al., 2021). These treatments may have resulted in lower fatality rate in this study than that in previous reports.

With this clinical information, characterization of the host genomic factors in

a representative sample of Japanese patients may provide insights into new treatment approaches.

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Ethics Approval:

This study was approved by the ethics committee of Keio University School of Medicine (20200061) and affiliated institutes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Japan COVID-19 Task Force are composed of more than 70 institutions nationwide in Japan. The members who contributed to the collection and analysis of cases at each institution are shown as coauthors in the following list.

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Table 1. Characteristics of 1674 patients with COVID-19 in Japan

Parameters	Number of patients with data	Subcategories	n (%) or median and IQR
Severity classification	1674		
		Asymptomatic	51 (3.0)
		Mild	933 (55.7)
		Severe	459 (27.4)
		Most severe	231 (13.8)
Death at discharge	1633		52 (3.2)
Age, years	1674		59 (45–71)
Sex	1674		
		Male	1109 (66.2)
		Female	565 (33.8)
Population	1674		
		Japanese	1629 (97.3)
		Others	45 (2.7)
BMI, kg/m^2	1525		23.9 (21.6–26.9)
Smoking history	1547		
		Never	840 (54.3)
		Previously or currently	707 (45.7)
Chronic medical conditions			
Hypertension	1643		569 (34.6)
Diabetes mellitus	1654		379 (22.9)
Coronary artery disease	1657		164 (9.9)
Malignancy	1640		97 (5.9)
Autoimmune disease	1653		61 (3.7)
COPD	1651		67 (4.1)
Chronic liver disease	1592		53 (3.3)
Chronic kidney disease	1579		110 (7.0)
Symptoms at referral			
Fever (≥37.5°C)	1653		1311 (79.3)
Cough	1648		959 (58.2)
Sputum	1642		405 (24.7)
Sore throat	1628		387 (23.8)

Rhinorrhea	1634		232 (14.2)
Dysgeusia	1635		305 (18.7)
Dysosmia	1634		278 (17.0)
Shortness of breath	1616		496 (30.7)
Fatigue	1642		811 (49.4)
Laboratory tests			
WBC [cells/μL]	1613		5200 (4100–6700)
LDH [IU/L]	1634		237 (190–314)
Ferritin [ng/mL]	1269		376 (171–711)
KL-6 [U/mL]	1213		234 (178–350)
PCT [ng/mL]	1165		0.06 (0.04–0.11)
CRP [mg/dL]	1628		2.69 (0.51–6.87)
Radiographic imaging			
Chest radiography findings	1556	Bilateral thoracic opacities	834 (53.6)
		Unilateral thoracic opacities	180 (11.6)
	1539	Bilateral thoracic consolidation	305 (19.8)
		Unilateral thoracic consolidation	121 (7.9)
Chest CT findings	1480	Bilateral GGO	1055 (71.3)
		Unilateral GGO	148 (10.0)
	1445	Bilateral consolidation	465 (32.2)
		Unilateral consolidation	110 (7.6)
Complications after referral			
Bacterial infection	1653		196 (11.9)
Heart failure	1641		36 (2.2)
Thrombosis	1623		59 (3.6)
COVID-19 treatment			
ICU admission	1650		314 (19.0)
Intubation	1649		183 (11.1)
ECMO	1641		37 (2.3)
Antiviral drugs			
	1657	Favipiravir	595 (35.9)
	1645	Ritonavir	7 (0.4)

	1648	Remdesivir	311 (18.9)
Hydroxychloroquine	1647		18 (1.1)
Tocilizumab	1643		118 (7.2)
Systemic corticosteroid	1663		680 (40.9)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease; CRP, C-reactive protein; CT, computed tomography; ECMO, extracorporeal membrane; GGO, ground glass opacity; ICU, intensive care unit; IQR, interquartile range; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; PCT, procalcitonin; WBC, white blood cell.

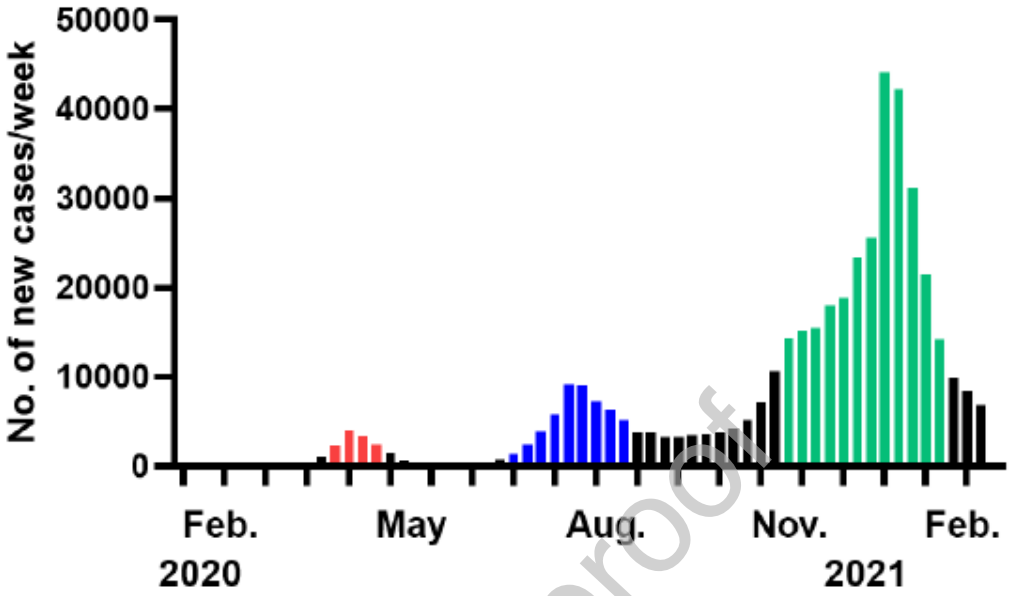

Figure 1. Coronavirus disease (COVID-19) epidemic trend in Japan, from February 2020 to February 2021. The epidemic curve shows the three epidemic waves during 1 year in Japan. ■Red bar shows the first wave including 89 patients in this study; from April 1 to 28, 2020. ■Blue bar shows the second wave including 468 patients in this study; from July 1 to September 1, 2020. ■ Green bar shows the third wave including 564 patients in this study; from November 18, 2020 to February 9, 2021. ■Black bar shows the number of new patients during the period not included in the three epidemic waves. We created this figure using GraphPad Prism 9 (GraphPad Software, San Diego, California).

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